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INTRODUCTION

In order for pregnancy to occur, an egg has to be released from the ovary and unite with a sperm. Normally this union, called fertilization, occurs within the fallopian tube. When this process cannot take place in the body, it can be accomplished in the laboratory by using the in vitro fertilization (IVF) technique. The technique, as currently practiced, involves uniting an egg(s) collected from a woman's ovary with sperm collected from her partner under laboratory conditions. The resulting normal embryo(s) may be transferred to the uterus (womb) for continued growth. The benefit of IVF and ET is that it gives a couple who may be unable to achieve a pregnancy an opportunity to attempt to overcome their infertility.

WHO WILL BENEFIT FROM IVF?

1. IVF is of demonstrated value for patients with absence or blockage of the fallopian tubes.
2. IVF is also recommended to those where corrective surgery has either failed and/or is deemed inadvisable.
3. Couples with infertility related to severe male factor, e.g., lowered sperm counts or motility or antisperm antibodies.
4. Those who have other causes of infertility such as: endometriosis, unexplained infertility, or couples that have experienced repetitive intrauterine insemination (IUI) therapy failure.

WHAT ARE YOUR CHANCES OF SUCCESS?

The probability of conceiving a child and delivering a healthy baby is very individual to each couple. Success has many variables such as: age, cause of infertility, the woman's response to fertility medications, the rate of the sperm's ability to fertilize the egg, the couple's willingness to undergo multiple embryo transfers, and the expertise of the chosen IVF program. Available at this website link SART (Society for Assisted Reproductive Technology) http://www.sart.org/ are the success rates for the IVF program at Wilford Hall Medical Center over the past five years. Look for our center under Texas and Lackland AFB.

SEVEN STEPS TO IVF

STEP # 1: PRELIMINARY TESTING

This includes, but is not limited to, an IVF consult at WHMC, a hysterosalpingogram (HSG) or office hysteroscopy, semen analysis and blood studies, including the clomiphene citrate challenge test.

All testing is usually completed prior to initiating an IVF cycle. If the results of any of the screening procedures are not satisfactory, the patient may be denied participation in the IVF Program. This requirement is to maintain the health and safety of the participants in the IVF Program.

BLOODWORK:

Female - Blood Tests
HIV, HbsAG, HcAb, RPR,
Blood Type-RH, Rubella, CBC
Prolactin, TSH, CCCT

Male - Blood Tests
HIV, HbsAG, HcAb, RPR

INFERTILITY CONSULT: One of the doctors on the infertility team will complete a history and physical examination at the time of consultation. It is helpful to bring copies of your old medical records and hysterosalpingogram films, if available.

HYSTEROSALPINGOGRAM: This is an X-Ray test of the uterus and fallopian tubes. If you have previously had a hysterosalpingogram or hysteroscopy the report and films should be brought to your appointment so your physician can review them. This test must be performed on days 7 - 10 of the menstrual cycle. Menstruation should be completed for this test to be done. You may experience some cramping during the procedure. It is recommended that you take ibuprofen (approximately 800 mgs) 1/2 hour prior to this procedure. This will reduce the cramping. If you cannot take ibuprofen, take 2 Extra-Strength Tylenol tablets instead.

CALL BACKS: IVF call backs will be made between 11:00 AM - 4:00PM on weekdays and from 10:00AM-2:00PM on Saturdays and Sundays. <u>If you will NOT be home, then you must have a telephone answering machine or cell phone with voice mail so that we may leave a message regarding your instructions.</u> If you do not receive a call back by 6:00PM on weekdays or 5:00PM on Saturdays or Sunday, please contact the Labor and Delivery unit at Wilford Hall Medical Center (210) 292-7410 and ask to speak to the chief resident on call.

A PERSONAL NOTE: The process of In Vitro Fertilization can be psychologically stressful. Significant anxiety and disappointment may occur. A substantial commitment of time by the couple is needed. Patients have described the IVF experience as an emotional roller coaster. Our IVF Program staff members are well aware of the added stress and burden that the IVF process can create. We, therefore, suggest that you consider joining a support group or participate in a therapy group to help you through this stressful period. If you would like additional information telephone the Wilford Hall Medical Center office at (210) 292-4016 and leave a message for , Ms. Frederika Rivera, our IVF coordinator.

LOCATION: RESOLVE support group…

Meetings:	Third Wednesday of each month
Time:	7:00 PM
Location:	North Central Baptist Hospital
Information:	(210) 961-6771

STEP # 2: DEVELOPMENT OF OOCYTES (EGGS)

It is necessary to stimulate the ovary with medications that develop multiple follicles (the cysts that contain the eggs), in order to improve your chances of a successful outcome from an IVF cycle. The IVF coordinator will meet with you and discuss the medication regimen and review the method and manner of medication administration. There are many different medication protocols that the physician may prescribe for you. This decision is based on factors such as your age, infertility history, past response to these medications, and baseline FSH level or CCCT results. The fertility medications that are necessary to stimulate the ovary are all injectable medications (except for Clomiphene Citrate, which is rarely used). You should refer to the package insert that accompanies these medications, for complete information concerning side effects and risks.

A. FERTILITY MEDICATIONS:

Follitropins:
This type of medication has been created using DNA recombinant technology. The hormone Follicle Stimulating Hormone (FSH) is now being produced in the laboratory. This is a relatively new class of drugs. In addition to consistency of dose, this medication may be given by the subcutaneous route (short needle).

Menotropins:
This type of medication is a purified preparation of the hormones Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). The hormones FSH and LH are naturally occurring in the urine of postmenopausal women. Some of these medications must be administered by the intramuscular injection (long needle), but others can be given subcutaneously.

Side Effects of Fertility Medications (Follitropins and Menotropins):

1. Overstimulation of the Ovary: The risk of Ovarian Hyperstimulation Syndrome (OHSS) increases as the estradiol levels in the blood increase and the number of follicles rises. OHSS can occur to varying degrees: mild, moderate or severe.

Signs & Symptoms:

Mild/Moderate - Abdominal bloating, ovarian enlargement, abdominal discomfort, weight gain (up to 10-15 pounds of fluid weight), nausea.

Severe -Large distended abdomen, severe abdominal pain, excessive weight gain (more than 20 pounds), shortness of breath, decreased urination, nausea and vomiting. Hospitalization is sometimes necessary for monitoring, fluid administration and administration of pain medication.

Cases of severe OHSS are more common and the condition lasts longer if pregnancy results from the IVF cycle. It is for this reason that based on your clinical situation (estradiol level, number of eggs retrieved, symptoms of severe OHSS) the physician may require that after all the eggs are retrieved and fertilized into embryos, all the embryos be frozen for future transfer. We understand that delaying the embryo transfer may be upsetting to you. The physician must consider all facts when making the decision that is best for your health. One comforting fact to remember is that the Wilford Hall Medical Center has an agreement with the Fertility Center of San Antonio to allow patients to freeze embryos for an additional charge. The Fertility Center of San Antonio's Frozen Embryo Pregnancy Rate is very similar to the Fresh Embryo Pregnancy Rate.
Careful and frequent monitoring of blood estradiol levels and ultrasound measurements of the number of follicles will assist the physician to prevent the occurrence of severe OHSS. Unfortunately, due to an unpredictable ovarian response, the risk of severe OHSS will still exist with the administration of fertility medication, despite the most vigorous monitoring efforts.

2. Multiple Births: The risk of conceiving a multiple pregnancy during an IVF cycle is dependent upon many factors. Factors such as your age, response to the medications, the quality of the embryos, the number of embryos replaced into the uterus and other unforseen factors are considered when judging your specific risk of multiple births. In the year 2006, 27 % of the women going through IVF had more than one live born infant. However, the percentage of women with a triplet pregnancy was 0%. We have not had any live birth quadruplet or higher order multiple pregnancies in over 12 years of IVF at our center.

3. Common complaints: Pain at the injection site, headaches, and fatigue.

A special note: You may have read reports that fertility drugs increase the risk of ovarian cancer. To date there are no conclusive studies that identify an association between taking fertility drugs and ovarian cancer. Ovarian cancer is the fifth most common type of internal organ cancer diagnosed in women. The average age of diagnosis is between 50 and 59 years of age.

Certain factors may be associated with an increased risk of ovarian cancer:
• Family history: For women with a family history of ovarian cancer, the increased risk may be as high as 50%.
• Pregnancy: Women that have successfully conceived a child-even if they have not had a successful birth- appear to have a lower incidence of ovarian cancer.
• Breast feeding and the use of oral contraceptives have been reported to be associated with a reduced risk of ovarian cancer.
• Environmental factors: The incidence of ovarian cancer is much higher in industrialized countries, leading to speculation that ovarian cancer may be associated with exposure to industrial byproducts in the environment.

B. GnRH AGONIST (Lupron) or ANTAGONIST (Ganirelix, Cetrotide)

This medication is administered by subcutaneous injection. It is given to prevent premature release of the oocytes (eggs). Side effects may include: localized skin reaction, allergic reaction, headaches, hot flashes and mood swings. If your scheduled menstruation is late while on Lupron, you should have a pregnancy test.

C. HCG (HUMAN CHORIONIC GONADOTROPIN)

You will be given instruction on the exact time this injection of medication should be taken. It is generally taken 34-36 hours prior to the egg retrieval. This medication should be injected into the muscle using a 1-1/2" needle. This medication completes the maturation of the egg. For mixing instructions, see the patient instruction sheet.

D. PROGESTERONE

You will begin taking this naturally occurring hormone the day after the egg retrieval. This medication causes the lining of the uterus to mature making implantation of the embryo possible. The side effects that have been reported with progesterone include: breast tenderness, headache, nausea, fluid retention, fatigue, mood swings, depression, and pain at the site of injection.
In 1977 the Food and Drug Administration (FDA) issued a warning that the use of progesterone may increase the risk of birth defects. As evaluated in our own research data, experience in our practice and the work of other researchers, there does not appear to be any increased risk of birth defects following use of progesterone. Moreover, the progesterone we use is the same formulation as the hormone that is naturally produced by a woman's own body each month after ovulation.

STEP # 3 : OOCYTE (EGG) RETRIEVAL

The egg collection process (egg retrieval) is usually accomplished using the ultrasound-guided trans-vaginal method. Other methods of retrieving oocytes that are rarely utilized in our practice but are sometimes necessary, include laparoscopy or a trans-abdominal approach.

The ultrasound-guided trans-vaginal method of egg retrieval allows this procedure to be done in an out-patient setting. A vaginal ultrasound allows for visualization of both ovaries. A needle is inserted through the vaginal wall into the ovary. Each follicle is punctured individually and the fluid containing the egg is drained and examined by the embryologist under the microscope until the egg is found. The duration of this procedure is usually less than 45 minutes.

A practice (mock) embryo transfer will normally be done after the egg retrieval. For the practice transfer, the physician inserts a tiny plastic catheter into the uterus. This allows the physician to measure the depth and direction of your uterus. For patient comfort, sedation is required. Conscious sedation is discussed below.

Conscious Sedation:
Conscious Sedation is administered by a Registered Nurse under the guidance and supervision of the physician. The patient is given a combination of two medications intravenously (IV): Versed which is in the valium family and Fentanyl which is in the morphine family. This type of sedation generally produces a "twilight sleep". The patient may be aware of her surroundings and the ongoing procedure. Response to sedation is very individual and therefore your comfort level with this type of sedation is difficult to predetermine.

STEP # 4: SPERM COLLECTION AND INSEMINATION

Before the egg retrieval is underway, the male partner will supply a semen sample. The specimen will be processed in our laboratory and prepared for egg insemination. Only the identified partner's sperm will be used to inseminate the eggs obtained from the female partner. Please discuss with the infertility staff any questions or concerns you may have prior to the day of egg retrieval. The male partner should abstain from ejaculation at least 48 hours prior to the retrieval but should not abstain from ejaculation longer than seven days prior to the egg retrieval

STEP # 5: INCUBATION AND FERTILIZATION OF OOCYTES (EGGS)

The eggs and sperm will be placed together in a special culture fluid and kept in incubators in our laboratory. This process is called insemination. The eggs will be examined 16-20 hours after insemination for signs of fertilization. If fertilization occurs, the fertilized eggs are now described as pre-embryos or zygotes. When they divide to at least 2 cells they are called embryos. The laboratory environment is conducive for fertilization to occur, however, it cannot be guaranteed that fertilization will occur. Typically, 60-80% of the eggs retrieved will be fertilized. This percentage may be higher or lower depending on each couple.. Sometimes the eggs will have to be injected with a single sperm to ensure fertilization. This process is called intracytoplasmic sperm injection (ICSI).

You will be contacted by the staff the morning after the retrieval. Information will be given regarding the number of eggs that fertilized and the future possibility for cryopreservation (freezing of embryos). You will also be reminded to start your progesterone and/or estrogen supplementation that evening.

STEP # 6: EMBRYO TRANSFER

Embryo Transfer (ET) usually occurs three days after the egg retrieval. The time of the transfer will be designated by the IVF staff. The embryos that are assessed to be developing normally will be considered for transfer. Although a recommendation of the number of embryos to transfer will be made by your physician (usually, 1-4 embryos depending on the woman's age and prior history), the final decision resides with the couple and the physician. Transferring multiple embryos may result in the growth of more than one fetus. If you have extra embryos after the transfer, they will be cryopreserved if they have demonstrated appropriate development and you have signed the consent for cryopreservation. Cryopreservation is an additional fee. Should transfer of the cryopreserved embryos be desired in the future, all cryopreserved embryos are thawed and transferred at the Fertility Center of San Antonio, by the Fertility Center of San Antonio's medical staff, not at Wilford Hall Medical Center.

The method used for transferring embryos is similar to that of the practice transfer. You will need to drink fluids to fill your bladder before the actual transfer so that we may visualize the uterus by ultrasound during the transfer. An embryo transfer is performed by inserting a small catheter through the cervical opening into the endometrial lining of the uterus. The embryo transfer is usually a painless procedure. There is a recommended rest period after the transfer. You will be given specific instructions prior to the transfer regarding your medications, future testing dates, and activity restrictions.

Within twelve days post-transfer, a pregnancy test will be done. If your pregnancy test is positive, further blood-work and an ultrasound will be required to assess progression of the pregnancy. Patients are generally followed in the infertility clinic throughout the first two months of the pregnancy and then referred to an Obstetrician.

STEP # 7: CRYOPRESERVATION (FREEZING) PROGRAM

The military does not permit us to store frozen embryos. The Fertility Center of San Antonio has graciously allowed our patients this service. All future activity with embryos frozen at Wilford Hall (thawing, transferring, etc) will be done at the Fertility Center of San Antonio.

The purpose of the Embryo Freezing Program is to give a couple participating in the IVF program the best chance to achieve a pregnancy with a maximum of safety. At the end of an IVF cycle there are often multiple embryos available for transfer. It has been found that transferring more than two embryos carries a significant risk of multiple pregnancy, while it does not increase the singleton pregnancy rate proportionately. The advantage of cryopreservation is that there may be an increased chance of pregnancy without the necessity of multiple stimulation cycles and oocyte retrievals. There are other advantages to embryo cryopreservation which include, but are not limited to: avoiding acute illness immediately following oocyte retrieval or other unforeseen conditions that would either prevent or make a fresh embryo transfer less than optimal. For example, if ovarian hyperstimulation syndrome seems likely to occur, all of the embryos should be frozen to prevent exacerbation of the condition, which may require hospitalization.

There are various stimulation protocols available to make a frozen transfer successful. You will be instructed by the physician which method may be best for your individual case. The frozen embryo transfer takes place in an identical manner to a fresh embryo transfer.

It must be realized that there is only minimal worldwide experience with prolonged human embryo storage. Currently, the longevity of embryos at -196°C is unknown. Extrapolating from information from other mammalian species, embryos that become healthy offspring can be stored up to ten years.

Embryos selected for cryopreservation will be frozen five to six days after the egg retrieval when they reach the blastocyst stage. The embryos will be placed in a cryopreserved media and frozen in a step-wise manner. At the end of the cryopreservation procedure the embryos will be stored frozen in tanks filled with liquid nitrogen. These cryopreserved embryos can be thawed and transferred at a future date. There is no guarantee of the survival of human cryopreserved thawed pre-embryos. If they have not survived, (as seen at the time of thawing), they will not be transferred. The Fertility Center of San Antonio, however, does have a very high survival rate for frozen embryos. We are pleased to offer our patients years of expertise in the area of cryopreservation. We are considered by many to have one of the most successful cryopreservation programs in the country.

There will be an additional cost for storage of cryopreserved embryos. Please refer to the following page for more details. You will receive in the mail a storage fee invoice until the time of transfer of the last stored embryo.

This booklet is intended to give you an overview of the human embryo cryopreservation program. The physicians and representatives of the IVF program encourage your questions. Please indicate to the IVF team, prior to oocyte retrieval, whether the concept of embryo cryopreservation is acceptable to you. Prior to actually freezing any embryos you will be asked to sign both a frozen embryo consent form and separate legal statement pertaining to disposition of cryopreserved embryos.

SPECIAL LABORATORY TECHNIQUES

ICSI - INTRACYTOPLASMIC SPERM INJECTION

This technique was developed in Brussels, Belgium at the Center for Reproductive Medicine in 1991. ICSI involves the injection of a single sperm directly into the cytoplasm of the oocyte (egg) using a technique called micromanipulation. This technique has revolutionized the treatment of male infertility. It is useful to couples where the male has a low sperm count, low sperm motility, high levels of anti-sperm antibodies or abnormal sperm morphology. In the case of testicular obstruction (ie: vasectomy), the sperm are aspirated from the epididymis or testes by the urologist and then the ICSI procedure is performed by the embryologist to fertilize the oocytes.

Careful follow up of all pregnancies are done and to date the rate of birth defects appears to be no higher than in naturally conceived children. It has been noted that men that have extremely low sperm counts may have a condition known as micro-deletion of the y-chromosome. This is a genetic condition that can account for why these men have a very low sperm count. This condition (micro-deletion of the y-chromosome) may be genetically passed down to the male offspring of this specific group of men. It has been shown that men with a condition called congenital absence of the vas deferens have a higher incidence of carrying the gene for cystic fibrosis and should have genetic testing done for cystic fibrosis.

Candidates for ICSI:

ICSI is useful for patients suffering from male factor infertility, which includes low count, low motility, abnormal sperm, high anti-sperm antibodies, or poor fertilization by conventional insemination in past cycles. ICSI requires very few total motile sperm, so even males with severe male factor infertility have a chance at producing a genetically related child. If there is an obstruction in the sperm ducts, a successful pregnancy can be achieved by collecting the fragile sperm from within the sperm duct behind the obstruction or from a testicular biopsy. Aspiration of the sperm from the male is performed by the Urology service at the Wilford Hall Medical Center on the same day that the eggs are retrieved.

Assisted Hatching

Assisted embryo hatching is a technique used in some IVF centers in women with a history of failed IVF cycles. A number of studies have suggested that some human embryos fertilized in-vitro lack the ability to "hatch" out of the embryo covering (zona pellucida). On the other hand, a number of studies suggest that assisted hatching is of no benefit in achieving pregnancy. This procedure is rarely recommended at WHMC.

UROLOGIC PROCEDURE ASSOCIATED WITH IVF

PESA-Percutaneous Epididymal Sperm Aspiration
MESA-Microsurgical Epididymal Sperm Aspiration
TESA- Testicular Sperm Aspiration

Certain forms of male infertility exist in which no sperm are retrievable from the ejaculated semen. This may be due either to an obstruction in the sperm ducts that lead from the testes, or to significantly reduced sperm production in the testes themselves.

To obtain sperm in such cases, sperm may be drained from the storage vessel just outside of the testis, the epididymis. This is known as PESA or MESA. When no sperm can be found in this region, an actual sample of tissue taken directly from the testis can be used to extract sperm for use in IVF/ICSI. This latter technique is known as a testicular biopsy. These procedures are performed by Urologists at Wilford Hall Medical Center. There is an additional embryology co-pay for couples who require this service.

Candidates for PESA/MESA or Testicular Biopsy are men diagnosed with:

- Congenital absence of the vas deferens
- Failed vasectomy reversal
- Low sperm production

EXPECTATIONS OF SUCCESS

Despite the encouraging statistics, it must be emphasized that successful conception and childbirth for any specific couple cannot be guaranteed by any IVF program, even if the couple undergoes multiple attempts. The probability of success depends on many factors, including, but not limited to, the patients age, the cause of infertility, and the skills and experience of the IVF team. (While almost all children resulting from human IVF have been normal, the possibility cannot be excluded that IVF could involve some unknown or increased risk to children who are conceived by this method.) Most infants who have been born following human in vitro fertilization have appeared healthy at birth. Animal offspring have usually been healthy following in vitro fertilization and/or embryo transfer. Yet, congenital abnormalities, birth defects, genetic abnormalities, mental retardation, and/or other possible deviations from normal may occur in children born following in vitro fertilization (as they may occur in children resulting from natural fertilization). At present there does not appear to be any increased risk of birth defects, though multiple births may be complicated by prematurity.

A pregnancy following IVF usually has a successful outcome but like any other pregnancy, may end in miscarriage or still birth. There is no evidence that the frequency of these events are increased by IVF. Even a tubal pregnancy is possible following IVF. There is also a greater chance of heterotropic pregnancy ie: one in the uterus and one in the fallopian tube. In this situation, the ectopic pregnancy will need to be surgically removed while every effort is made to preserve the intrauterine pregnancy.

HOW CAN YOU MAKE THIS IVF CYCLE THE MOST SUCCESSFUL IT CAN BE?

- • Stop Smoking: Many studies have suggested that smoking cigarettes decreases the pregnancy rate. If you are unable to stop smoking entirely, a decrease in the number of cigarettes you smoke in a day will have a positive effect especially during the time period after the embryos are transferred.

- • Limit Medications: Tylenol (Acetominophen) is the only medication that may be taken without prior discussion with the IVF staff. Many other medications are acceptable to take but some medications are dangerous. Aspirin, Motrin, Advil, Naproxen, Alieve, to name a few, should never be taken during an egg retrieval cycle.

- • Maintain normal body weight: For optimal results, a woman should not be more than 20% over her ideal bodyweight.

- • Avoid Alcoholic Beverages: Males and females should not drink more than two alcoholic drinks per day prior to the egg retrieval. After the embryo transfer, the female partner should refrain from all alcoholic beverages.

- • Avoid Hot Tubs/Steam Rooms: It has been shown that excessive heat is detrimental for the motility of the sperm and a fetus in utero. Males should avoid excessive heat at least 90 days prior to the egg retrieval and females should abstain after the embryo transfer.